

REMARKS

Applicants acknowledge that the Examiner has renumbered the claims. Applicants respectfully request confirmation that the Examiner amended the dependencies of the claims to reflect the renumbering.

In the above amendment, claims 1, 3, 15, 20, and 24 have been amended. Upon entry of the amendment, claims 1, 3, 6-8, and 13-25 will remain pending in this application. Reconsideration of the merits of this application is respectfully requested in light of the above amendment and the following remarks.

No new matter has been added as a result of the claim amendments. Support for the amendments will be discussed in the remarks below.

Objections

The Examiner objected to the amendment filed January 8, 2002 because it allegedly introduced new matter. Specifically the Examiner stated that the following amendments were not supported by the original disclosure:

1. Harvesting nucleated cells from peripheral blood or CD-34+ cells,
2. Or other immature/early progenitor cells from blood containing multipotent stem cells,
3. Wherein the immunotoxin is directed to epitopes on a combination of these.

Applicants respectfully traverse this objection.

Support for the objected to language can be found in claim 1 as originally filed in the PCT application. Claim 1 of the PCT application, of which the current application is a national stage filing, reads as follows:

1. Method for killing unwanted target cells in a cell population wherein the cell population comprises nucleated cells harvested from peripheral blood, or CD-34⁺ cells selected from the above nucleated cells, or CD-34⁺ cells harvested from bone marrow aspirates, or other immature/early progenitor cells from bone marrow or blood containing multipotent stem cells, or malignant cells supported by normal stromal cells, characterized in that the cell population is exposed to one or more immunotoxins, wherein each immunotoxin is composed of a conjugate between an antibody and a cell toxin, fragments of antibodies and toxin, or recombinantly produced antibodies, toxins, immunotoxins or fragments thereof.

Support for the objected to language can be found in claim 1 of the PCT application. As such, the objected to language does not introduce new matter. Accordingly, Applicants assert that cancellation of the language objected to should not be required. A determination to this effect is earnestly solicited.

Rejections Under 35 USC 112, First Paragraph

Claims 1, 6-8, 13-14, 20-23, and 25-26 have been rejected under 35 USC 112, first paragraph as allegedly lacking an enabling disclosure. Applicants respectfully traverse the rejection.

The Examiner stated:

One cannot extrapolate the teaching of the specification to the scope of the claims because both EPG2 and MUC1 are ubiquitously expressed in normal cells and it would be expected that any immunotoxins, other than those specific for the antigens expressed on tumor cells would be sequestered by the ubiquitously expressed antigens on normal cells. Thus, it could not be predicted that a sufficient concentration of immunotoxins would become bound to tumor cells so that the invention would function as claimed.

However, the Examiner appears to misunderstand the differences between the antigens expressed on tumor cells and normal cells. The Examiner is correct in pointing out that EPG2 and MUC1 are also present on normal cells, but one skilled in the art would recognize that immunotoxins, e.g. BM7-PE and MOC31-PE, would be more toxic to tumor cells than to normal cells. This is

the case with nearly all chemotherapeutics, which may be toxic to normal cells. In the case of immunotoxins directed to EPG2 and MUC1 antigens, which are expressed on both tumor and normal cells, one would expect that the immunotoxins would be more toxic to tumor cells. There are at least two reasons for the increased toxicity towards tumor cells. First, as the abstracts of the references cited by the Examiner (Apostolopoulos et al. and McClaughlin et al.) indicate, tumor cells express these antigens at a higher level than normal cells. Accordingly, more immunotoxin would be expected to bind and be internalized by tumor cells than normal cells. Second, internalization of immunotoxin would be expected to occur at a faster rate in tumor cells than normal cells. The slower internalization of immunotoxin by normal cells leads to a decomposition of the immunotoxin before it enters the cell cytoplasm. Therefore, tumor cells would be expected to not only more rapidly (relative to normal cells) internalize an immunotoxin bound to EPG2 or MUC1, but also express higher levels (relative to normal cells) of the antigen. As such, one can readily predict that immunotoxins directed to these antigens would be more toxic to tumor cells than normal cells. Yet, as discussed below, one could not have predicted just how well immunotoxins directed to these antigens would work in combination.

The Examiner further stated,

although one would expect that other types of carcinomas expressing the same epitopes would be killed, it cannot be predicted that other antibodies to the claimed antigens would have the same effect, especially since it appears that both MOC31 and BM7 (the only disclosed antibodies which thus have 'high specific activity' for the tumor antigens) are selective for antigen expressed on tumor cells.

Again, the Examiner appears to misunderstand the differences between the antigens expressed on tumor cells and normal cells. As the Examiner pointed out, EPG2 and MUC1 antigens are present on normal cells as well as tumor cells. The ability of MOC31-PE and BM-7-PE to preferentially kill tumor cells is likely do to the higher level of expression of the EPG2 and MUC1 antibodies and more rapid internalization of the antibody, not because MOC31 and BM7 are selective for antigen expressed on tumor cells. These antibodies recognize antigen expressed on both tumor cells and normal cells. However, the immunotoxins are toxic to tumor cells at concentrations that are not toxic to normal cells.

Further, the specification at Table 1, page 8, shows that the combination of MOC31 with not only BM7, but also BM2, produced surprisingly greater than additive effects in killing breast cancer cells. In fact, BM2, which was less effective on its own than was BM7, proved to be a bit more effective than BM7 when used in combination with MOC31 (see Table 1). Accordingly, the specification teaches the combination of immunotoxins directed towards the MUC1 and EPG2 antigens can surprisingly kill tumor cells in a more than additive manner than the individual immunotoxins alone. The specification teaches that the combination surprisingly works well for immunotoxins that have differing activity when used alone. As such, the specification teaches that the combination of immunotoxins with antibodies directed towards the MUC1 and EPG2 antigens produces surprisingly high toxic activity toward tumor cells.

The Examiner also stated that the abstract of the McLaughlin reference teaches that MOC31 antibody "specifically localizes to EGP2-positive tumors and does not localize in normal cells." The abstract goes not to propose that the reason for the differential localization is one of accessibility. However, as stated above, MOC31 recognizes the EPG2 antigen on both normal and tumor cells. One would expect that a MOC31-PE immunotoxin would be more toxic to tumor cells than normal cells for the reasons addressed above. The abstract of the McLaughlin reference provides yet another reason why a MOC31-PE immunotoxin may preferentially kill tumor cells.

Finally the Examiner stated, "Applicant has not addressed the issue raised drawn to the restriction against MOC31 for any purpose other than research since the claims are drawn to treatment and not to research." Applicant respectfully reminds that Examiner that use of a compound, including antibodies, for treatment often requires approval from an appropriate regulatory agency. The determination of whether to approve the use of an immunotoxin, and thus make the MOC31 antibody available and marketable for therapeutic purposes, is a determination to be made by an administrative agency other than the Patent and Trademark Office. It would be inappropriate for the Examiner to reject the present claims because MOC31 is currently being sold for research purposes, as therapeutic use of a MOC31 based immunotoxin has not been approved.

In light of the above remarks, withdrawal of the rejection is respectfully requested.

Claims 3, 15, 16, 18, and 19 were rejected under 35 USC 112, first paragraph. The Examiner asserted that the antibody BM7 is no longer publicly available. Applicants respectfully traverse the rejection to the extent that it is maintained.

Claims 3 and 15 have been amended to recite "BM2" rather than "BM7". Claims 18, 18, and 19 are dependent on amended claim 15. As amended, claims 3, 15, 16, 18, and 19 refer to the antibody BM2 rather than BM7. As BM2 is a publically available antibody that can be readily obtained, and as the claims no longer recite BM7, withdrawal of the rejection is respectfully requested.

Claims 1, 3, 6-8, 20, and 24-36 were also rejected under 35 USC 112, first paragraph, as the specification allegedly does not contain a written description of the claimed invention. The Examiner stated that the language of a "method for killing breast cancer cells or other carcinoma cells ... in a cell population comprising nucleated peripheral blood cells" has no clear support in the specification and the claims as originally filed. Applicants respectfully traverse the rejection. Support for the referred to language can be found in claim 1 as filed in the PCT application (see above). Withdrawal of the rejection is respectfully requested.

Claims 20, 21 and 25 were also rejected under 35 USC 112, first paragraph, as the specification allegedly does not contain a written description of the claimed invention. Applicants respectfully traverse the rejection to the extent that it is maintained.

The Examiner stated that the language "relatively high toxicity" and "relatively low toxicity" of claim 20 and the language "low toxicity" of claims 24 (it is believed that the Examiner intended for this rejection to apply to claims 20 and 24 rather than 20, 21 and 25) has not support in the specification. Claims 20 and 24 have been amended to recite "toxicity" and "is not toxic."

Support for the claimed language can be found throughout the specification. For example, at page 11, lines 1-5, the specification discloses the surprising result that combinations of immunotoxins directed to antigens expressed on epithelial cells killed malignant cells without performing any damage on normal stem cells. At page 24, lines 20-25, it is further stated that an immunotoxin mixture killed all tumor cells without toxicity to normal cells. Additionally, results presented in Table 6 on page 21 show an example of the effectiveness of an immunotoxin mixture in killing breast cancer cells in the presence of peripheral blood progenitor cells (PBPCs), while Table 7 on page 23 shows that the immunotoxin mixture is not toxic to the

PBPCs. The specification provides support for the amended claimed language "toxic" and "non-toxic".

Withdrawal of the rejection is respectfully requested.

Rejections Under 35 USC 112, Second Paragraph

Claims 3, 15, 16, 18 and 19 have been rejected under 35 USC 112, second paragraph as allegedly being indefinite. The Examiner asserted that the antibody BM7 is no longer publicly available. Applicants respectfully traverse the rejection to the extent that it is maintained.

Claims 3 and 15 have been amended to recite "BM2" rather than "BM7". Claims 18, 18, and 19 are dependent on amended claim 15. As amended, claims 3, 15, 16, 18, and 19 refer to the antibody BM2 rather than BM7. As BM2 is a publicly available antibody that can be readily obtained, and as the claims no longer recite BM7, withdrawal of the rejection is respectfully requested.

Claims 1, 3, 6, 7, 8, 20, 24, 25, and 26 have been rejected under 35 USC 112, second paragraph as allegedly being indefinite. Applicants respectfully traverse the rejection to the extent that it is maintained.

The Examiner stated that the claims were indefinite because claim 1 recited the phrase "a recombinantly produced antibodies." Claim 1 has been amended to correct a typographical error. Claim 1 now recites "a recombinantly produced antibody." Applicants assert that the claim as amended is clear and definite. Withdrawal of the rejection is respectfully requested.

Claims 1, 3, 6, 7, 8, 20, 24, 25, and 26 have been rejected under 35 USC 112, second paragraph as allegedly being indefinite. Applicants respectfully traverse the rejection.

The Examiner stated that the claims were indefinite because claim 1 recites "active toxin fragments" and "[i]t is not clear what activity those fragments have ...". The term "active toxin fragment" would be clear and definite to one skilled in the art upon reading the specification. One skilled in the art understands that *Pseudomonas* exotoxin A has is toxic to cells due to its inhibition of protein synthesis. One of skill in the art also understands that fragments of *Pseudomonas* exotoxin A (PE) can also inhibit protein synthesis and be toxic to cells. In its natural state, PE typically includes a fragment that binds the extracellular surface of a cell, which allows the fragment to be internalized and allows the active fragment to inhibit protein synthesis. In an immunotoxin, the fragment responsible for binding the toxin to the cell may not be require

as the antibody can serve this function. However, in an immunotoxin, a PE fragment that has toxic activity would be required. Otherwise the immunotoxin would not be toxic to the cell, defeating the purpose of the immunotoxin. Accordingly, one of skill in the art, upon reading the specification, would clearly and definitely understand that active toxin fragments are those fragments that possess toxic activity towards cells. Withdrawal of the rejection is respectfully requested.

Claim 20 has been rejected under 35 USC 112, second paragraph as allegedly being indefinite. Applicants respectfully traverse the rejection to the extent that it is maintained.

The Examiner objected to the claim language "relatively high toxicity" and "relatively low toxicity". The claims have been amended to recite "toxicity" and "is not toxic", respectively. The claims as amended are definite. Withdrawal of the rejection is respectfully requested.

Obviousness Rejection

Claims 1, 13, 14, and 24 have been rejected as allegedly being obvious for the reasons previously set forth in Paper No. 20, Section 9, pages 5-7 drawn to the rejection of claims 1 and 14. Applicants respectfully traverse the rejection.

Specifically, the Examiner stated that "only one example of synergy is presented wherein synergy is noted with antibodies selective for epitopes expressed on tumor cells but not on normal cells." As stated above, the specification provides examples of multiple immunotoxin combinations that surprisingly show a synergistic toxic effect towards cancer cells but not normal cells. For example, the specification at Table 1, page 8, shows that the combination of MOC31 with not only BM7, but also BM2, produced surprisingly greater than additive effects in killing breast cancer cells.

In addition, the Examiner's belief that MOC31 and BM7 selectively bind tumor cells is mistaken. As indicated above, MOC31 and BM7 bind both tumor cells and normal cells that express MUC1 and EPG2 antigens. The selective toxic effect of immunotoxins towards tumor cells rather than normal cells is predictable and likely due to higher antigen expression on tumor cells and/or increased rate of internalization of the immunotoxin. However, it is unexpected and surprising that a combination of immunotoxins directed to MUC1 and EPG2 antigens produces a more than additive toxic effect against tumor cells relative to individual immunotoxins alone. Accordingly, the claimed invention is not obvious.

Withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicants respectfully assert that the claims, upon entry of this amendment, are in a condition for allowance, and earnestly solicit a notice to that effect.

Applicants believe all of the outstanding objection and rejections have been addressed. If the Examiner has any questions regarding the foregoing, it is respectfully requested that she call the undersigned.

Respectfully Submitted,

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1. (Amended) Method to kill breast cancer cells or other carcinoma cells expressing the same target antigens in a cell population selected from the group consisting of cells comprising nucleated cells in peripheral blood and bone marrow cells comprising CD-34⁺ cells selected from the above nucleated cells, the method comprising:

incubating the cell population with a combination of two or more immunotoxins, wherein each immunotoxin comprises a conjugate between an antibody or antigen binding antibody fragments and a cell toxin or active toxin fragments, or a recombinantly produced [antibodies] antibody or antigen binding antibody fragments, and toxins or active toxin fragments, wherein the antibodies or antigen binding antibody fragments are directed to epitopes on the antigen EGP2 expressed by the gene GA733-2 and to epitopes on the antigen expressed by the MUC1 gene and the toxin is Pseudomonas exotoxin A.

3. (Amended) The method according to claim 1, wherein the antibodies are MOC31 and [BM7] BM2, or antigen binding fragments thereof.

15. (Amended) The method according to claim 14, wherein the first immunotoxin comprises a PE molecule conjugated to a MOC31 antibody or an antigen-binding antibody fragment thereof, and the second immunotoxin comprises a PE molecule conjugated to a [BM7] BM2 antibody or an antigen-binding antibody fragment thereof.

20. (Amended) The method according to claim 1 wherein treatment of the cell population with the two or more immunotoxins causes [relatively high] toxicity to cancer or carcinoma cells and [relatively low toxicity] is not toxic to CD34⁺ cells in the population.

24. (Amended) The method according to claim 1 wherein treatment of the cell population with the two or more immunotoxins [causes low toxicity] is not toxic to CD34⁺ cells in the population.